REMARKS

Claims 17, 18, 36-56, 58-60, 71-78, 84-90 and 95-117 were pending in the application. Claims 17, 18, 36-50, 52, 54, 58, 60, 74, 76, 85, 87, 90, 99, 101, 105, 107, 113 and 115 have been cancelled. Claims 51, 55, 56, 59, 71, 77, 78, 84, 86, 88, 89, 95, 102-104, 108, 109, 112, 116, and 117 have been amended. New claims 118-121 have been added. Accordingly, claims 51, 53, 55, 56, 59, 71-73, 75, 77, 78, 84, 86, 88, 89, 95-98, 100, 102-104, 106, 108-112, 114, and 116-121 are pending following entry of this amendment.

Support for the amendments to claims 51, 55, 56, 59, 71, 77, 78, 84, 86, 88, 89, 95, 102-104, 108, 109, 112, 116 and 117 can be found in the claims as originally filed and throughout the specification. Additional support for the amendments to claims 51, 71, and 84, 95, 104 and 112 can be found in the specification at least at page 29, lines 8-24. Support for the term "mammal" in amended claim 51 can be found in the claims as originally filed and in the specification at least at page 14, lines 31-32. Support for the term "inhibiting a humoral immune response" in claim 71 can be found in the specification at least at page 10, lines 15-26. Support for new claim 118 can be found in the claims as filed and in the specification, at least at page 29, lines 10-15. Support for new claims 119-121 can be found in the claims as filed and in the specification, at least at page 30, lines 10-12. No new matter has been added.

Amendments to the claims should in no way be construed as acquiescent to any of the Examiner's rejections and were made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

The Examiner communicates that claims 95-117 have been "withdrawn from consideration as drawn to an invention that is independent or distinct from the invention originally claimed." The Examiner further states that "[a]s such, the newly submitted claims would require different searches and the consideration of different patentability issues." Applicants respectfully request clarification of the Examiner's position for the record. As the Examiner fails to cite to the Rules of Practice or the United States Code, Applicants are unable to respond to this position. Accordingly, Applicants respectfully request that the Examiner clarify the basis for this position in the next Office Action on the merits.

Withdrawal of Certain Rejections

Applicants gratefully acknowledge the withdrawal of the rejection of claims 53, 58-60, 71-78, and 84-90 under 35 U.S.C. 112, second paragraph as well as the withdrawal of the rejection of claims 51-60, 71-78, and 84-90 under 35 U.S.C. 112, first paragraph.

Rejection of Claims 53, 58-60, 75, 86, and 90 Under 35 U.S.C. § 112, First Paragraph, Written Description

The Examiner has rejected claims 53, 58-60, 75, 86, and 90 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the invention at the time the application was filed. The Examiner states, "[T]here does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of a fragment of SEQ ID No: 1." The Examiner also states, "Applicant does not appear to have reduced to practice any functional fragment of SEQ ID No: 1." Applicants respectfully traverse this rejection.

Claim 53 is directed to a method of inhibiting a humoral immune response in a subject by administering a pharmaceutical composition comprising an effective amount of a soluble lymphotoxin-beta receptor (LTβR) comprising at least one ligand binding domain that can selectively bind to a surface LT ligand fused to one or more heterologous protein domains, wherein the ligand binding domain comprises SEQ ID NO: 1, or a functional fragment thereof. Applicants' specification provides ample disclosure for one of ordinary skill in the art to identify the composition of such an agent. The present application teaches inhibition of a humoral immune response in a subject *via* administration of soluble LTβR agents. Both the specification and claim 53 make clear that a functional soluble LTβR agent of the invention is one that contains at least one ligand binding domain of LTβR (refer to the present specification, at least at page 32, lines 23-27). As defined in the specification at page 14, lines 20-23, "[t]he term "LTβ-R ligand binding domain" refers to the portion or portions of the LTβ-R that are involved in specific recognition of and interaction with a LT ligand." At page 15 of the present specification, Applicants additionally have described the TNF family of ligands and their associated receptors, to which surface LT and the LTβR respectively belong, and have indicated

that the topology and functional domains of LTβR were known to one of ordinary skill in the art at the time of filing. (Indeed, characterization of the sequence and functional domains of human and mouse LTβR were performed by Crowe et al. (Reference CL of the IDS) and Force et al. (Reference CU of the IDS), both referenced by the present specification.)

At page 29 of the instant specification, Applicants further teach how to produce the soluble LTβR molecules of the present invention. Applicants present the sequence of the extracellular portion of human LTβR in Figure 1 of the instant application and describe this sequence as containing the ligand binding domain of LTβR. The present specification at page 30, lines 1-5 additionally states that "[a]ll or a functional portion of the LTβ-R extracellular region (Figure 1) comprising the LTβ-R ligand binding domain may be fused to an immunoglobulin constant region like the Fc domain of a human IgG1 heavy chain [Reference CH of the IDS]." Based on the descriptive sections of the specification and the state of the art at the time, one of ordinary skill in the art would be capable of envisioning the full scope of the claimed soluble forms of LTβR.

Applicants additionally describe the use of two separate forms of soluble LTβR as working examples within the present specification. Examples 1 and 2 of the present specification (refer to pages 58-60) detail the synthesis of human and murine soluble LTβR agents, respectively. The murine soluble LTβR-Ig molecule was then employed in Examples 3-7 of the present specification. The human and murine soluble LTβR agents featured in the instant invention were additionally described in Applicants' previously co-pending 08/505,606 application (now the '351 patent; refer to page 29, line 18 of the present specification), as well as in Browning et al. (Reference CH of the IDS). At page 31, lines 15-31 of the instant specification, Applicants further describe deposit in the American Type Culture Collection (ATCC) of distinct CHO cell lines that secrete soluble human LTβR-Fc and soluble murine LTβR-Ig fusion proteins, respectively. Thus, at the time of filing, Applicants were additionally in possession of working examples of presently claimed agents comprising soluble LTβR fused to a heterologous protein domain.

In light of both the state of the art and the teachings of the specification, one of ordinary skill in the art additionally would have recognized Applicants to be in possession of the genus encompassed by "SEQ ID NO: 1, or a functional fragment thereof", as presently claimed. Indeed, the topology and functional domains of LTβR were known to one of ordinary skill in the art, as described in the present specification. Having knowledge of the LTβR sequence (comprising SEQ ID NO: 1 of the present specification) and ligand binding domain structure of LTβR, one of ordinary skill in the art at the time of filing would have recognized Applicants' possession of soluble forms of LTβR as encompassing the full scope of soluble forms of LTβR molecules that comprise at least one intact ligand binding domain. Thus, there is sufficient description in the specification as well as knowledge in the art at the time of filing to convey to one of ordinary skill in the art that Applicants were in possession of the soluble LTβR agents of the presently claimed invention.

As the Examiner is aware, according to the PTO's own written description guidelines, the written description requirement does *not* require that a representative number of species of a claimed genus be "reduced to practice" but rather, simply requires that a representative number be disclosed. Indeed, there is no basis in the law to require Applicants to provide *any* working examples to satisfy the written description requirement (though Applicants have provided such working examples in the present specification). Furthermore, "a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (see MPEP 2163(II.A.3.a.ii). Here, Applicants have, in fact, fully disclosed their possession of two working examples of soluble LTβR fusion proteins and have described the scope of compositions encompassed by the term "a functional fragment" of soluble LTβR (e.g., SEQ ID NO: 1) in the present written description. Applicants' teachings, in combination with the advanced state of the art with respect to knowledge of the functional domain structure of soluble LTβR, would have conveyed to one of ordinary skill in the art that Applicants were in possession of the invention as presently claimed. Applicants therefore submit that the written description requirement set forth

in 35 U.S.C. 112, first paragraph is satisfied and the Examiner is requested to reconsider and withdraw this rejection.

Rejection of Claims 51-56, 58-60, 71-78 and 84-90 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 51-56, 58-60, 71-78 and 84-90 under 35 U.S.C. § 102(e) as being anticipated by US Patent 5,925,351 (herein '351). Applicants respectfully traverse this rejection.

The '351 patent teaches the use of LTβR blocking agents (e.g., a soluble LTβR agent) for inhibiting ***Th1 cell-mediated immune responses*** (including, e.g., delayed type hypersensitivity responses, inflammatory bowel disease, etc.). The present application teaches the use of LTβR blocking agents for manipulation and treatment of ***non-Th1 cell mediated responses*** and conditions. Specifically, claim 51 of the present invention claims a method for inhibiting a humoral immune response in an animal *via* administration of a soluble LTβR agent. At page 12, lines 8-13 of the present specification, the term "humoral response" is defined as the "immunological response of an animal to a foreign antigen whereby the animal produces antibodies to the foreign antigen. The Th2 class of T helper cells are important to the efficient production of high affinity antibodies." Claims 51-60 are thus directed to inhibition of a non-Th1 cell-mediated response. Similarly, as presently amended, claim 71 claims a method of inhibiting a humoral immune response by inhibiting LT-β receptor signaling without inhibiting TNF-R signaling using the LTβR agents of the present invention. Claims 71-78 are thus directed to inhibition of a non-Th1 cell-mediated response. Claim 84 claims a method of disrupting the association of immune complexes and B cell follicles through use of the LTβR agents of the present invention. Description of the effect of LTβR agents on immune complexes and B cell follicles is novel to the present specification and is not classified as a Th1 cell-mediated response. Claims 84-90 are therefore directed to disruption of a non-Th1 cell-mediated response. Because the present application teaches methods of use of LTβR agents for manipulation and treatment of non-Th1 cell mediated responses and conditions, the claims of the present invention are novel over the '351 patent.

In conclusion, the claims of the present invention are directed to methods of modulating or treating non-Th1 cell-mediated responses and diseases, *via* administration of a soluble LTβR agent. As the '351 patent teaches methods of inhibiting Th1 cell-mediated immune responses

using LTβR blocking agents, the presently claimed subject matter is novel in view of the '351 patent. Thus, it is respectfully requested that the present 35 U.S.C. § 102(e) rejection be reconsidered and withdrawn.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. BGNA013 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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